Claim amendments

Claims 1 and 15 have been amended to indicate that the receptor molecule is capable of binding to a TNF trimer in a stoichiometric ratio of 1:1. Support for the amendment can be found, for example, on page 18, lines 23-24 of the instant specification. Claim 14 has been amended in accordance with the helpful suggestions of the Examiner.

Claims 27-37 have been added. Claim 27 relates to the receptor molecule of Claim 1 wherein the tumor necrosis is of human origin and the polylinker is a polyglycine linker sequence. Support for Claim 27 can be found, for example, on page 6, lines 3-4 and page 7, line 18. Claims 28-37 relate to receptor molecules comprising the specific sequences provided in the instant specification, *i.e.,* SEQ ID No: 1 and SEQ ID No:2.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures

The Examiner states that the "application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821 (a)(1) and (a)(2)" (Office Action, page 2). However, the Examiner states that this application fails to comply with the requirements of 37 C.F.R. § 1.821-1.825 for the reasons set forth on the attached Notice to Comply.

A Transmittal of Substitute Sequence Listing and Preliminary Amendment which included a copy of the Notice and which complies with the Sequence Rules was received in the U.S. Patent and Trademark Office on September 29, 2000 for filing in the subject application.

Rejection of Claims 1-3, 6, 8, 15-17 and 19-26 under 35 U.S.C. §103(a)

Claims 1-3, 6, 8, 15-17 and 19-26 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Wallach *et al.*. U.S. patent No. 5,478,925" (Office Action, page 2) or "as being unpatentable over Wallach *et al.*. EP 0 526 905" (Office Action, page 3), referred to herein as

Wallach *et al.*. The Examiner states that Wallach *et al.* teach "multimers of TNFR moieties, each such moiety corresponding to a soluble TNFR polypeptide"; that "because both TNF and its receptors function *in vivo* as trimers, the multimeric receptors will be more effective than monomeric soluble receptors in binding to and inhibiting TNF"; that "dimers or trimers of the TNF moieties may be advantageously made"; that "the monomers should be separated by linker moieties of 'optimum length . . . to produce multimers which best bind TNF' and that '[t]hose of ordinary skill in the art will be able to determine' such optimum length"; that 'the nature of the amino acids which link the monomers in the recombinantly produced multimer is not critical'"; that "multimers may be conveniently made as contiguous fusion proteins by recombinant methods . . ., incorporating signal sequences as appropriate to the host cell system employed"; and that "the multimers are suitable for the treatment of various TNF-mediated diseases and disorders, including septic shock, cachexia, GVHD, and various autoimmune diseases including rheumatoid arthritis" (Office Action, pages 2-3). The Examiner states that Wallach *et al.* do not teach "the preparation of any particular fusion multimer, nor does it specify the amino acid sequences of the TNFR monomers or the linker peptides" (Office Action, page 3). It is the Examiner's opinion that:

> [i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to make a fusion protein comprising two or three human p55 and/or p75 TNFR extracellular domain sequences, joined by suitable linker sequences and optionally comprising a signal sequence for production in an appropriate host cell, because Wallach teaches that it is advantageous to do so. In the course of making such fusions, it would have been obvious to construct DNA encoding the fusion polypeptide by excising the TNFR sequences from vectors available in the art, ligating them, and transforming suitable host cells, and to obtain the fusions by expression in the transformed host cells, because Wallach teaches that the fusions it describes are conveniently made by such methods. Finally, it would have been obvious to use the fusion proteins thus produced to inhibit TNF, as in treatment of diseases including particularly rheumatoid arthritis, because Wallach teaches that the multimers are advantageously employed for such purposes. The claimed invention would have been *primae facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary (Office Action, page 3).

Applicants respectfully disagree. Wallach *et al.* prepared multimers of the soluble form of TNF-R using chemical cross-linking methods. As noted by the Examiner and as pointed out in the previous Amendment mailed to the Patent Office on January 5, 1998 for filing in the

parent application (U.S. Application No. 08/437,533), Wallach *et al.* did not prepare a fusion multimer and did not specify the sequences of the TNF monomers or the linker peptides. Wallach *et al.* disclose that recombinant techniques can be used to prepare the multimers , but specifically teach that "the nature of the amino acids which link the monomers in the recombinantly produced multimer is *not critical*" (Wallach *et al.*, column 4, lines 29-31, emphasis added).

Applicants compared the protective effects of their claimed dimeric TNF receptor to a fusion protein in which dimeric p75 TNF-R ECD was fused to an Ig backbone. Applicants found that 20 pg of their dimeric receptor were sufficient to inhibit by 50% the killing activity of human TNF, however, 57 pg of the dimeric p75 TNF-R fused to the Ig backbone were required to produce the same effect. Applicants teach that:

> [t]he concentration of 20pg/ml Hu p75 TNF-R ECD dimer needed to inhibit by 50% the cytotoxic effect of 62.5 pg/ml TNF indicates that this antagonist is capable of binding to the TNF homotrimer in a stoichiometric ratio of almost 1:1 (specification, page 18, lines 22-24).

Clearly, the linker is critical for function of Applicants' claimed receptor molecule. As amended, Applicants' claimed invention relates to a receptor molecule which binds to TNF comprising all or a functional portion of two extracellular domains of TNF receptors linked to a polypeptide linker, wherein said polypeptide linker is covalently bonded to said extracellular domains via peptide bonds and wherein the receptor molecule is capable of binding to a TNF trimer in a stoichiometric ratio of almost 1:1.

Wallach *et al.* do not teach that the amino acids which link the monomers in multimer are critical and do not teach that their receptor molecule is capable of binding to a TNF trimer in a stoichiometric ratio of almost 1:1.

Wallach *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

Objection to Claim 14

Claims 14 "is objected to as depending from rejected base claims but would be allowable if rewritten in independent form, including all of the limitations of base claim 1 and intervening claim 8" (Office Action, page 4).

Claim 14 has been amended in accordance with the Examiner's suggestion.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J. Collins

Anne J. Collins
Registration No. 40,564
Telephone (781) 861-6240
Facsimile (781) 861-9540

Lexington, Massachusetts 02421-4799
Dated: March 28, 2001

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Please amend Claims 1, 14 and 15 as follows:

1. (Twice amended) A receptor molecule which binds to tumor necrosis factor comprising all or a functional portion of two extracellular domains of tumor necrosis factor receptors linked to a polypeptide linker, wherein said polypeptide linker is covalently bonded to said extracellular domains via peptide bonds and wherein the receptor molecule is capable of binding to a tumor necrosis factor trimer in a stoichiometric ratio of almost 1:1.

14. (Amended ) [The] Isolated DNA [of Claim 8] comprising a receptor molecule which binds to tumor necrosis factor comprising all or a functional portion of two extracellular domains of tumor necrosis factor receptors linked to a polypeptide linker, wherein said polypeptide linker is covalently bonded to said extracellular domains via peptide bonds and wherein the DNA comprises SEQ ID NO: 1.

15. (Twice amended) A method of making a construct which expresses a receptor molecule which binds to tumor necrosis factor comprising all or a functional portion of the extracellular domain of two or more tumor necrosis factor receptors linked to a polypeptide linker, wherein the receptor molecule is capable of binding to a tumor necrosis factor trimer in a stoichiometric ratio of almost 1:1, comprising the steps of:

g) obtaining a first vector which expresses all or a functional portion of an extracellular domain of a first tumor necrosis factor receptor and a signal peptide of a secreted protein;

h) obtaining a second vector which expresses all or a functional portion of an extracellular domain of a second tumor necrosis factor receptor; and

i) ligating the first vector of (a) to the second vector of (b) using a coding sequence for a polypeptide linker

so that the first vector of (a) is linked to the second vector of (b) using the coding sequence for the polypeptide linker resulting in a construct which expresses all or a functional portion of the extracellular domain of the first tumor necrosis factor receptor and all or a portion of the extracellular domain of the second tumor necrosis factor receptor linked using the polypeptide linker.